



King's Research Portal

DOI:

[10.1016/j.crad.2018.10.007](https://doi.org/10.1016/j.crad.2018.10.007)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Pencharz, D., Dunn, J., Connor, S., Siddiqui, A., Sriskandan, N., Thavaraj, S., Jeannon, J-P., Oakley, R., Lei, M., Guerrero-Urbano, T., Cook, G. J., & Szyszko, T. A. (2018). Palatine tonsil SUVmax on FDG PET-CT as a discriminator between benign and malignant tonsils in patients with and without head and neck squamous cell carcinoma of unknown primary. *Clinical Radiology*. <https://doi.org/10.1016/j.crad.2018.10.007>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Palatine tonsil SUVmax ratio on FDG PET-CT as a discriminator between benign
and malignant tonsils in patients with and without head and neck SCC of unknown
primary

Deborah Pencharz¹, Joel Dunn², Steve Connor³, Ata Siddiqui³, Neshe Sriskandan³, Selvam
Thavaraj⁴, Jean-Pierre Jeannon³, Richard Oakley³, Mary Lei³, Teresa Guerrero-Urbano³, Gary
J. Cook², Teresa A. Szyszko²

This work originates from: King's College London and St Guy's and St Thomas' PET Centre,
London, UK

1 Department of Nuclear Medicine, Brighton and Sussex University Hospitals NHS Trust,
Brighton, UK

2 King's College London and St Guy's and St Thomas' PET Centre, London, UK

3 Guy's and St Thomas' NHS Foundation Trust, London, UK

4 Head and Neck Pathology King's College London

1: Corresponding author. Department of nuclear medicine, Royal Sussex County Hospital,
Eastern Road, Brighton, BN2 5BE East Sussex, UK. Deborah.pencharz@bsuh.nhs.uk
+447545077713.

None of the authors have any conflicts of interest or financial disclosures to make.

No grants were received in the preparation of this paper.

No other acknowledgements need to be made

Abstract

Aims:

¹⁸F-FDG PET/CT is used to identify the primary site in head and neck SCC of unknown primary. Tonsils are an important potential primary however accurately distinguishing physiological from malignant tonsillar uptake can be challenging. We analysed the SUVmax ratio between tonsils in patients with and without tonsillar carcinoma to determine useful diagnostic thresholds.

Materials and Methods:

PET/CTs of patients with suspected head and neck SCC and in controls from April 2013 - September 2016 were retrospectively reviewed. Tonsillar SUVmax ratio (ipsilateral/contralateral for malignant tonsils, maximum/minimum for patients without (controls)) was calculated and used to construct a ROC curve.

Results:

Twenty-five patients had tonsillar carcinoma: mean, range of the SUVmax ratio was 2.0, 0.89 - 5.4. There were eighty-six controls with mean, range of the SUVmax ratio of 1.1, 1 - 1.5. Using the ROC, the most accurate SUVmax ratio for identifying malignancy was > 1.2 (77% sensitivity, 86% specificity). A potentially more clinically useful SUVmax ratio is ≥ 1.6 with 62% sensitivity and 100% specificity.

Conclusion:

An SUVmax ratio between tonsils ≥ 1.6 is highly suspicious for SCC and could be used to direct site of biopsy. Some malignant tonsils had normal FDG uptake therefore PET/CT should not be used to exclude tonsillar cancer. Minor asymmetrical uptake is frequently seen in non-malignant tonsils and does not necessarily require further investigation. Due to the single centre nature of this study and

the recognised variation in SUV measurements between PET scans other centres may need to develop their own cut-offs

Introduction

Head and neck (HN) squamous cell carcinoma (SCC) can present with neck lumps from cervical lymph node metastases, the presence of which is usually confirmed with fine needle aspiration (FNA). If no primary is identified by outpatient examination of the head and neck (HN) and CT and/or MRI then the patient is determined as having a cancer of unknown primary (CUP) of the HN (1). However identification of the primary tumour is important both for accurate staging and because optimum treatment for patients with CUP is uncertain. Some centres treat the neck disease alone however others will treat some or all potential primary sites with radiotherapy +/- chemotherapy (2).

Recent guidelines have recommended F-18-fluorodeoxyglucose (FDG) Positron Emission Tomography – Computed Tomography (PET-CT) as the imaging investigation of choice to non-invasively attempt to detect the primary tumour (1, 2). In terms of PET/CT's ability to diagnose a palatine tonsillar primary, Davison et al. (3) compared the uptake in malignant and contralateral tonsils and found that the maximum standardised uptake value (SUVmax) ratio between sides had a better diagnostic accuracy (area under the receiver operating characteristic (AUROC)) than SUVmax alone and SUVmax difference between tonsils.

However there is a discrepancy in the literature on the recorded range of tonsillar SUVmax ratio in patients with and without palatine tonsillar SCC. Davison et al. (3) reported a complete separation of the ranges of SUVmax ratio between the groups with malignant and non malignant tonsils but Lee et al. (4) reported an overlap. Whether or not there is overlap between the ranges is important as it affects the certainty with which PET-CT can be used to predict the presence or absence of tonsillar carcinoma. More in line with Lee et al's (4) findings, in the centre this study was performed in, we have observed patients who had normal FDG uptake within their palatine tonsils who later had a tonsillar SCC proven on biopsy.

The primary aim of this study was therefore to analyse FDG PET-CT scans of patients being evaluated for HN CUP and to analyse the SUVmax ratio between tonsils of patients with and without tonsillar carcinoma. This would allow the identification of SUVmax ratios which could be used to predict the likelihood of the presence or absence of tonsillar SCC.

Patients referred for FDG PET-CT for non HN indications may also show incidental asymmetrical FDG uptake in their tonsils, leading to a concern this could represent an incidental primary tonsillar malignancy. A secondary aim was therefore to identify the range of SUVmax ratios in patients with suspected HN CUP who did not have tonsillar SCC and in an additional group of patients referred for non HN indications. This would facilitate more accurate PET-CT reporting and patient management when asymmetrical incidental tonsillar FDG uptake is observed.

Methods

This was a retrospective analysis of palatine tonsillar appearances of patients who were referred for a FDG PET-CT scan as part of their routine clinical care. Approval for the research was gained from the institution at which it was performed but separate ethics approval and patient consent were not required and data were kept fully anonymised.

Patient Selection

The FDG PET-CT scans of all patients who had been referred with clinical codes of 'unknown primary' referred by the head and neck team between April 2013 and September 2016 were retrieved. Patients who had their FDG PET-CT scan after panendoscopy and biopsy were excluded. Patients with previous tonsillectomy that was not due to cancer were included as SCC can arise in the tonsillar remnant (5) and the patients' tonsillectomy status is frequently unknown at the time of

PET-CT reporting. N=79 patients fitted the inclusion criteria. N=25 patients were diagnosed with a tonsillar primary (tonsil group) and n=50 patients had confirmed non-tonsillar primary (control group 1). Not all patients in control group 1 had HN SCC, however these patients were still included as the results of FNA and the final diagnosis is frequently not known at the time of PET-CT reporting. Excluding these patients would therefore result in the study not being a true representation of the PET-CTs referred and reported for potential HN CUP.

Three patients were excluded as they had pathological uptake from a non-tonsillar primary site extending into the tonsil and one patient was excluded as they had had previous tonsillar carcinoma and were referred with a second HN primary.

The FDG PET-CT scans for a non HN control group of 36 patients (control group 2), referred for variety of non HN indications (such as lymphoma, lung cancer or non-malignant pathologies) were analysed, three patients from each calendar month from July 2015 – June 2016 (control group 2). Patients with lymphoma, where there was any suspicion of tonsillar involvement, were excluded. Patients were selected equally across the calendar year to account for any possible change in tonsil appearances due to seasonal variation in viral upper respiratory tract infections

PET-CT image acquisition and SUV measurements

Patients fasted for 6 hours. Blood glucose was measured prior to scanning to check this was within the range of 4 to 8 mmol/L. Patients were injected with 350 MBq of FDG and after an uptake time of 90 minutes they were scanned on GE Discovery 710 PET-CT scanners in 3D acquisition mode. Patients were first scanned with a head and neck protocol from midbrain to lung apex, with arms down, supine, head first, at 2 bed positions, 3 minutes per bed and an overlap of 11 slices. Once completed, a second PET scan immediately followed with a half-body protocol (6-9 bed positions, 3-4 minutes per bed, 11 slice overlap). Non-contrast helical CT was obtained for attenuation correction

and localisation prior to each PET scan, with tube voltage 140kV, detector coverage 40mm (64 x 0.625mm), helical thickness 2.5mm, pitch 1.375, rotation speed 0.5s. CTs for head and neck scans had a fixed beam current of 70mA, and modulated current (SmartmA, noise index = 40, range 15-100 mA) for the halfbody scan. PET images were reconstructed using the iterative time of flight algorithm (GE Vuepoint FX) with voxel sizes 2.73 x 2.73 x 3.27mm. CT images were reconstructed with the adaptive statistical iterative (ASiR) algorithm.

SUV accuracy was maintained with a quarterly scanner normalisation and cross calibration of the PET scanners with the dose calibrator, daily checks on the cross calibration and an annual check of the patient scales accuracy.

Image analysis

Regions of interest (ROIs) were manually drawn around both tonsils and the SUVmax within each tonsil recorded using Hermes Gold 3 (Sweden) software. The SUVmax ratio between tonsils was calculated where:

$$\text{SUVmax ratio} = \text{SUVmax of ipsilateral tonsil} / \text{SUVmax of contralateral tonsil}$$

The ipsilateral tonsil was considered to be the tonsil on the same side as the pathological lymph nodes for the tonsillar carcinoma group. For the control groups 1 and 2, the tonsil with the highest SUVmax was considered the 'ipsilateral' tonsil.

We also looked at CT features on low dose unenhanced CT. In patients with tonsillar SCC, CT appearances of the tonsils were recorded using the following categories: 1 = no asymmetry, 2 = mild asymmetry (asymmetry is present but, on CT appearances alone, it is not possible to accurately

determine whether or not the asymmetry is likely to be pathological or physiological) 3 = definite asymmetry (based on CT appearances alone it is highly likely to be pathological).

Statistical methods

GraphPad Prism (v7.03, <http://www.graphpad.com/>) was used to perform statistical analysis. The mean and standard deviation of the SUVmax ratio of the three groups of patients were calculated. ROC curves were constructed and used to determine the area under the curve (AUC) and the optimal cut-off for the detection of tonsillar primary (defined as the minimum of the sum of squares of 1-sensitivity and 1-specificity, equivalent to the point nearest the top left corner of the ROC curve).

The Shapiro-Wilk test was used to test normality of SUVmax ratios in each group. SUVmax ratios in all three groups were found to deviate significantly from normality and this was not improved with a log-transform, hence non-parametric methods were used to analyze the data. The Kruskal-Wallis test was conducted to assess for any difference in SUVmax ratio between the three groups, with Dunn's test with multiple comparison corrections used to establish differences in mean rank between pairs of groups.

Results

Patient demographics for the three groups of patients is shown in Table 1:

The final diagnosis for control group 1 is shown in Table 2

Tonsil SUVmax, SUVmax ratio and CT appearances and are shown in table 3

Kruskall-Wallis test revealed a highly significant difference in SUVmax ratio between the three groups (Kruskall-Wallis statistic 27.0, $p < 0.0001$). Post-hoc Dunn's test (with multiple comparison corrections) showed highly significant differences in mean rank between the tonsil group and control group 1 ($p < 0.0001$) and between tonsil group and control group 2 ($p < 0.0001$). No significant difference was established between the control groups ($p = 1.0$).

Figures 1 and 2 are examples of patients with FDG avid tonsillar SCC and of CT appearances of the tonsils classified as 1 and 2

Three patients with tonsillar carcinoma had completely normal uptake with SUVmax ratios of 0.89, 1.0 and 1.1, the PET-CT appearances for one of these patients is shown in figure 3.

Figure 4 shows the range, interquartile range and median for the SUVmax ratio between tonsils in all three groups of patients. As expected the median and range is much higher in the malignant group and the two control groups appear quite similar.

Figure 5 shows the ROC curve for the use of tonsillar SUVmax ratio for the diagnosis of tonsillar carcinoma. The AUROC is 0.83 (CI 0.71-0.96). The optimal cutoff ratio is 1.2 which has a sensitivity of 77% and a specificity of 86%. However, a potentially more clinically useful cut off SUVmax ratio with a 100% positive predictive value is ≥ 1.6 . This has a sensitivity of 62% and specificity of 100%.

Discussion:

SUVmax ratio and PET-CT appearances of tonsillar carcinoma

We have identified a range of SUVmax ratio in patients with proven tonsillar SCC of 0.89 – 5.44. This is nearly identical to the range reported by Lee et al. (4) of 0.85 – 5.45 but different to the range of 1.48 – 8.31 reported by Davison et al. (3) This is an important finding as it provides further evidence that there is an overlap in the range of SUVmax ratio between malignant and non-malignant tonsils and that PET/CT cannot be used to exclude tonsillar carcinoma.

However an SUVmax ratio ≥ 1.6 has 100% specificity and PPV for malignancy therefore this SUVmax ratio could be used to predict that the tonsil is a likely primary site. This could obviate the need for panendoscopy and directed biopsies and the associated morbidity in terms of pain, dysphagia and bleeding risk. This ratio of ≥ 1.6 is similar to the SUVmax ratio of 1.48 which had 100% specificity reported by Davison et al. (3), although they reported a 100% sensitivity for this ratio and we have found a sensitivity of 62%. The difference in sensitivity between our study and Davison et al is likely because Davison et al only analysed patients with known tonsillar SCC, they do not specify if they included patients who initially presented with CUP. The poor sensitivity of 62% should not be a cause for concern because, when imaging has not detected a primary tumour, according to UK guidelines(1), the patient should still proceed to panendoscopy, directed biopsies and bilateral tonsillectomy and this would ensure that a tonsillar primary will still be detected if it exists.

All three patients who had no detectable increased FDG uptake in their malignant tonsil had T1 disease. This can help explain why they were FDG negative, it is expected that smaller tumours are more likely to have lower uptake of FDG due to technical factors such as partial volume effects, the 6-8mm resolution of PET and count rate statistics. Only mildly detectable increased FDG uptake that could occur in small tumours may also be more difficult to detect when it is occurring in the tonsils that frequently have normal physiological increased FDG uptake. Higher false negative rates in smaller tumours was also found by Lee et al.(6) who reported false negative results on FDG PET-CT in 22.3% of patients with T1 HN SCC but only 2.2% of T2 tumours.

Additionally HPV positive primary tumours have been found to demonstrate lower FDG avidity than HPV negative tumours. (7) Although a limitation of this study is that we have not looked at human papillomatous virus (HPV) status in all lesions we did record that the three patients with no detectable increased FDG uptake in their malignant tonsil were all positive for HPV.

A more minor but further useful finding from this study is that normal CT appearances should not be used as evidence there is not a tonsillar primary as 56% of patients with tonsillar carcinoma had no CT asymmetry and a further 20% had only very mild asymmetry. Although it should be noted these were unenhanced, low dose CTs and that the discriminatory power of CT on diagnostic contrast enhanced CT may be better.

SUVmax ratio of non-malignant tonsils

The range of tonsillar SUVmax ratios is 1.0 – 1.48 in patients with HN pathology and 1.0 – 1.28 in patients without. These results are similar to Davison et al. (3) who reported an SUVmax ratio range of 1 -1.48 in their control group of patients with non-tonsillar HN SCC and to Lee et al. (4) who reported 0.86 – 1.25 in patients with non-tonsillar HN SCC and 1.01 – 1.49 in patients without cancer but with risk factors for HN SCC.

We have therefore provided additional evidence that mild asymmetrical tonsillar FDG uptake occurs in a population without tonsillar carcinoma or other HN pathology. Taking into account other published ranges, the upper limit of this ratio is 1.5. However, as we have also shown, there is no SUVmax ratio which can exclude tonsillar carcinoma. Therefore, using an upper limit of SUVmax ratio to choose not to further investigate, could, rarely, miss a tonsillar carcinoma. However a limit is still required to prevent unnecessary intervention and biopsy/tonsillectomy in a large proportion of the population who do not have tonsillar carcinoma.

Limitations

When using SUVs to guide management it is important to be aware that differences in scanner type and reconstruction techniques can produce different SUVs. In particular the use of point spread function, time of flight (8) and newer algorithms which allow fully convergent PET image reconstruction but without excessive noise (9) have all been shown to increase the SUV, particularly in smaller lesions which is pertinent to the tonsils. This might have an effect on ratios if the reconstruction effect is greater in FDG avid tissue. Different uptake times and body mass index can also affect SUVs (10).

Another potential limitation is that this is a single centre study and we measured the SUVmax ratio in a relatively small sample of patients and controls. However our results are very similar to the published studies described above demonstrating that our results are still likely a good representation of the patient and control population. As already mentioned, we have not looked at HPV positive and negative lesions separately and this would be an interesting area of future work.

Due to the limitations described above we suggest that other centres may need to develop their own cut-offs of SUVmax ratio between tonsils to help discriminate between benign and malignant tonsils.

Conclusion

1. The palatine tonsillar SUVmax ratio in patients with histologically proven tonsillar SCC was 0.89 – 5.4. This is consistent with a previously published result and provides further evidence that FDG PET-CT cannot be used to exclude the presence of a tonsillar primary SCC. However it could be used to conclude there is a tonsillar primary, obviating the need for panendoscopy and directed biopsies. We suggest a ratio of ≥ 1.6 is used for this purpose which had a 100% PPV in our study.

2. Patients without tonsillar carcinoma or other HN pathology can have mildly increased SUVmax ratios and an upper limit is required when deciding when to further investigate patients in whom asymmetrical tonsillar uptake is incidentally observed. In line with other studies, we suggest an upper limit of 1.5.

References

1. Mackenzie K, Watson M, Jankowska P, Bhide S, Simo R. Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130(S2):S170-S5.
2. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. NICE Guideline 36 Full guideline February 2016: National Collaborating Centre for Cancer; 2016 [Available from: <https://www.nice.org.uk/guidance/ng36/evidence/full-guideline-2307980269>.
3. Davison JM, Ozonoff A, Imsande HM, Grillone GA, Subramaniam RM. Squamous cell carcinoma of the palatine tonsils: FDG standardized uptake value ratio as a biomarker to differentiate tonsillar carcinoma from physiologic uptake. Radiology. 2010;255(2):578-85.
4. Lee HJ, Kim JS, Roh JL, Lee JH, Cho KJ, Park GC, et al. Utility of quantitative 18 F-fluorodeoxyglucose uptake measurement to identify occult tonsillar carcinoma in patients with cervical metastasis of unknown primary tumours: a retrospective case-control study. Clin Otolaryngol. 2013;38(1):30-8.
5. Skilbeck CJ, Jeannon JP, O'Connell M, Morgan PR, Simo R. Squamous cell carcinoma of the tonsillar remnant--clinical presentation and oncological outcome. Head Neck Oncol. 2011;3:4.
6. Lee HS, Kim JS, Roh JL, Choi SH, Nam SY, Kim SY. Clinical values for abnormal ¹⁸F-FDG uptake in the head and neck region of patients with head and neck squamous cell carcinoma. Eur J Radiol. 2014;83(8):1455-60.
7. Tahari AK, Alluri KC, Quon H, Koch W, Wahl RL, Subramaniam RM. FDG PET/CT imaging of oropharyngeal squamous cell carcinoma: characteristics of human papillomavirus-positive and -negative tumors. Clin Nucl Med. 2014;39(3):225-31.
8. Akamatsu G, Mitsumoto K, Taniguchi T, Tsutsui Y, Baba S, Sasaki M. Influences of point-spread function and time-of-flight reconstructions on standardized uptake value of lymph node metastases in FDG-PET. Eur J Radiol. 2014;83(1):226-30.
9. Reynés-Llompart G, Gámez-Cenzano C, Romero-Zayas I, Rodríguez-Bel L, Vercher-Conejero JL, Martí-Climent JM. Performance Characteristics of the Whole-Body Discovery IQ PET/CT System. J Nucl Med. 2017;58(7):1155-61.
10. Mahmud MH, Nordin AJ, Ahmad Saad FF, Azman AZ. Impacts of biological and procedural factors on semiquantification uptake value of liver in fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging. Quant Imaging Med Surg. 2015;5(5):700-7.

Table 1: Patient demographics for the SCC and Control Groups

Patient Characteristics	Tonsillar SCC group (n=25)	Control group 1	Control group 2 (no HN pathology)

		(suspected HN SCC, non tonsillar primary) (n=50)	(n=36)
Age (years) mean, range	61, 48 - 72	64, 28 – 92	62, 27 – 87
Gender			
Male (%)	69	71	50
Female (%)	31	29	50

Table 2: Final diagnoses for the patients in control group 1.

Diagnosis	Percentage
Base of tongue SCC	16
HN SCC of 'true' unknown primary	12
Piriform fossa SCC	4
Oropharynx SCC (but not tonsil)	2
Supraglottic SCC	4
Vocal cord SCC	2
Vallecula SCC	2
Olfactory neuroblastoma	2
Nerve sheath tumour	2
Salivary gland pathology (parotid cancer, pleomorphic adenoma)	6
Thyroid cancer	6
Non HN malignancy ^a	28
No malignancy found ^b	14

a Lung cancer, oesophageal cancer, lymphoma, prostate cancer, endometrial cancer, poorly differentiated adenocarcinoma, skin SCC, melanoma

b after comprehensive work up including FNA of neck lump if present

Table 3: SUVmax and the range, mean and standard deviation of the SUVmax ratio for malignant tonsils and controls.

	SUVmax of tonsils	Range of Ratio (I/C) (max/min)	Mean (S.D.) of Ratio	CT appearances of tonsil group
Malignant tonsils N=25	3.3 – 18.3	0.89 – 5.44	2.0 (1.17)	1 = 56%, 2 = 20% 3 = 24%
Control group 1 (with HN SCC) n=50	2.1 – 11.4	1.00 – 1.48	1.1 (0.10)	
Control group 2 (non HN SCC) n=36	2.0 – 9.7	1.00 – 1.28	1.1 (0.07)	

Figure Legends

Fig. 1 A left sided tonsillar primary SCC with normal CT appearances

Fig. 2 A right sided tonsillar SCC with mildly increased FDG uptake and mild soft tissue asymmetry on CT (CT appearances 2)

Fig. 3 PET and CT images of patient A, described above, with normal FDG uptake within a right tonsillar tumour. Increased FDG uptake in right sided metastatic lymph nodes can also be seen.

Fig. 4 Box and whisker plot (showing the median, interquartile range and range) of SUVmax ratio between tonsils in the three groups of patients

Fig. 5 ROC curve of tonsil SUVmax ratio in patients with suspected HNSCC (tonsil group vs control group 1). Optimal cut-off point is shown in red.